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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/747,521	12/21/2000	Darrel R. Galloway	22727/04079	9991

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EXAMINER	
DUFFY, PATRICIA ANN	
ART UNIT	**PAPER NUMBER**
1645	

DATE MAILED: 09/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/747,521	GALLOWAY ET AL.	
	Examiner	Art Unit	
	Patricia A. Duffy	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *5-24-05, 7-1-05 and 9-5-05*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24,26,27,31,41,42,45-50 and 53-55* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24, 26, 27, 31, 41, 42, 45-50 and 53-55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 September 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)

2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3)☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2005*.

4)☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

5)☐ Notice of Informal Patent Application (PTO-152)

6)☐ Other: _____.

SDD

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after allowance or after an Office action under *Ex Parte Quayle*, 25 USPQ 74, 453 O.G. 213 (Comm'r Pat. 1935). Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 7-1-05 has been entered.

Please note that the examiner in charge of this application has changed.

Priority

Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged. However, the provisional application upon which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for claims 24, 26, 27, 31, 41, 42, 45-50 and 53-55 of this application.

The provisional application does not provide any written description or contemplate LF mutant proteins or fragments thereof that lack metalloproteinase activity. As such, this application only entitled to the instant filing date for prior art purposes. Should Applicant wish to dispute this finding, they should point to the provisional document 60/171,459 by page and line number where written description support can be found for the instantly claimed invention.

Drawings

The drawings were received on 9-5-05. These drawings are acceptable and resolve the outstanding issue with regard to "1C" and "2C".

Information Disclosure Statement

The information disclosure statement filed 5-24-05 has been considered. An initialed copy is enclosed.

Claim Objections

Claims 46 and 48 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The claims recite that the mammalian expression vectors is a eukaryotic expression plasmid. The genus of eukaryotic is broader than mammalian and therefore claims 46 and 48 are not seen to properly further limit the claim. This issue may be resolved by reciting that the mammalian expression vector is a plasmid.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 24, 26, 27, 31, 41, 42, 45-50, 53-55 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification broadly describes as part of the invention isolated polynucleotides comprising the "LF protein" (see pages 5-6, bridging paragraph) for use as a vaccine. The specification also broadly describes a "mutant LF protein " specifically by a reference to a specific mutation E687C known to the art (see page 13, second full paragraph) and a truncated LF protein consisting of residues 42 to 285 of SEQ ID NO:2. The specification teaches a single truncated LF protein of Figure 1. The specification broadly describes polynucleotides encoding the LF protein of Figure 1, to specifically include sequence variants in which one or more of the amino acids in the LF protein reference sequence is substituted, or in which one or more amino acids are deleted from or added to such sequence (see paragraph bridging page 5-6). Applicants also broadly describe the invention as embracing any substitution, insertion or deletion change of nucleotides throughout the entire stretch of nucleotides found in the encoding or reference sequence (see pages 5 and 6) by use of language in which a specified percent of amino acids can be changed in the polypeptide. It is noted that the specification defines LF protein at page 5 and indicates that it encompasses naturally occurring and mutated LF proteins whose sequence differs from that shown in Figure 1. The art does not teach the genus of naturally occurring LF proteins and the specification provides for unlimited mutation of the LF protein of Figure 1. Neither the specification nor the art provides for description of any naturally occurring mutations of Figure 1. The specification does not provide written description of the nucleic acids encoding such. As such, the specification lacks sufficient written description to provide possession of the claimed genus encoding naturally occurring mutants or mutated *B. anthrasis* lethal factor proteins per se or those

lacking metalloproteinase activity or fragments thereof. Therefore, the highly limited teachings of the specification directed to contemplation of a specific nucleic acid sequence encoding a specific LF protein of the prior art, having the property of lacking metalloproteinase activity does not support possession of the now claimed genus. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). The actual structure or other relevant identifying characteristics of each nucleic acid that encodes a variant protein having the claimed properties of an mutant LF protein can only be determined empirically by actually making every nucleic acid that encodes the a mutant and testing each to determine whether it encodes a protein having the particularly disclosed properties of an LF protein. As noted in the Guidelines at Section I.A.(2):

> There is an inverse correlation between the level of predictability in the art and the amount of disclosure necessary to satisfy the written description requirement. For example, if there is a well-established correlation between structure and function in the art, one skilled in the art will be able to reasonable predict the complete structure of the claimed invention from its function.

Applicants specification proposes the converse, yet still does not meet the requirements for an adequate written description of the claimed invention. Applicants propose that the skilled artisan is to modify a known nucleic acid sequence encoding a known protein sequence and that modification would still describe applicants' invention as a LF protein as disclosed. The LF protein of Figure 1 of the specification has specific biological properties dictated by the structure of the protein and the corresponding structure of the structural gene sequence which encodes it. There must be some nexus between the

structure of a gene sequence and the structure of the protein encoded, and the function of that encoded protein. However, function cannot be predicted from the modification of the structure of the gene or in this case the gene encoding the protein. Applicants have not shown that, by modifying a reference sequence encoding a reference polypeptide as claimed, will automatically predict the production of a LF protein. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. Herein, claims directed to the genus of mutants and fragments thereof are unpatentable due to lack of written description for the broad class. It is well recognized that in the "unpredictable" fields of science, it is appropriate to recognize the variability in the science in determining the scope of the coverage to which the inventor is entitled. Such a decision usually focuses on the exemplification in the specification. See, e.g., Enzo Biochem, 296 F.3d at 1327-28 (remanding for district court to determine "[w]hether the disclosure provided by the three deposits in this case, coupled with the skill of the art, describes the genera of claims 1-3 and 5"); Lilly, 119 F.3d at 1569 (genus not described where "a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus" had not been provided); In re Gostelli, 872 F.2d 1008, 1012 (Fed. Cir. 1989) (two chemical compounds were insufficient description of subgenus); In re Smith, 458 F.2d 1389, 1394-95 (CCPA 1972) (disclosure of genus and one species was not sufficient description of intermediate subgenus. Similarly, here the genus of LF protein mutants is vast and includes additions, deletions and substitutions while the specification discloses a single specific mutation at a specific position that lacks metalloproteinase activity. Thus, the contemplation of a vast genus of LF mutants and one

LF mutant species lacking metalloproteinase activity is not sufficient to describe or provide written description for the contemplation of the intermediate subgenus now claimed. Thus, the specificaiton as originally filed does not provide conception by way of written description of a subgenus of LF mutants lacking metalloproteinase activity. There is no conception of different changes to position 687 of lethal factor, other than that particularly change disclosed. There is no conception of changes to residue 720 as claimed in claim 31. There is no conception of the genus of "an amino acid other than glutamic acid" at position 687 or any other position. There is no conception of the subgenus of polynucleotides encoding mutants lacking metalloproteinase activity as now claimed. Further, Klimpel et al (1994) of record indicates that replacement of glycine (E) at positions 720 and 721 with alanine had no effect on LF activity (see abstract). Applicants mix and match different concepts in the specification to arrive at a subgenus that is not conceived of by way of written description in the specification as filed and apparently claim a mutant which has metalloproteinase activity according to the art. With the exception of an isolated polynucleotide consisting of amino acid residues 42-285 of SEQ ID NO:2 the skilled artisan cannot envision all the contemplated nucleotide sequences by the detailed chemical structure of the claimed polynucleotides and therefore conception cannot be not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation.

Similarly, the specification broadly describes as part of the invention isolated polynucleotides comprising the "PA protein" (see page 7, first and second paragraph) for use as a vaccine. The specification teaches a single nucleic acid encoding the PA protein as set forth in Figure 2 (SEQ ID NO:4). The specification broadly describes polynucleotides encoding the PA protein of Figure 2, to specifically include sequence variants in which one or more of the amino acids in the LF protein reference sequence is substituted, or in which one or more amino acids are deleted from or added to such sequence (see first and second paragraph top of page 7) by means of percent identity. Applicants also broadly describe

the invention as embracing any substitution, insertion or deletion change of nucleotides throughout the entire stretch of nucleotides found in the encoding or reference sequence (see page 7) by use of language in which a specified percent of amino acids can be changed in the polypeptide. It is noted that the specification defines PA protein indicating that it encompasses naturally occurring and mutated PA proteins whose sequence differs from that shown in Figure 2 (SEQ ID NO:4). The art does not teach the genus of naturally occurring PA proteins or encoding nucleic acids and the specification provides for unlimited mutation of the PA protein of Figure 2. Neither the specification nor the art provides for description of any naturally occurring mutations of Figure 2. The specification does not provide written description of the nucleic acids encoding such. As such, the specification lacks sufficient written description to provide possession of the claimed genus encoding naturally occurring mutants or mutated *B. anthrasis* protective antigen and fragments thereof. Therefore, the highly limited teachings of the specification directed to a specific nucleic acid sequence encoding a specific PA protein and specific fragment thereof does not support possession of the now claimed genus. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). The actual structure or other relevant identifying characteristics of each nucleic acid that encodes a variant protein having the claimed properties of an mutant PA protein can only be determined empirically by actually making every nucleic acid that encodes the a mutant and testing each to determine whether it encodes a protein having the particularly disclosed properties of a PA protein. As noted in the Guidelines at Section I.A.(2):

> There is an inverse correlation between the level of predictability in the art and the amount of disclosure necessary to satisfy the written description requirement. For example, if there is a well-established correlation between structure and function in the art, one skilled in the art will be able to reasonable predict the complete structure of the claimed invention from its function.

Applicants specification proposes the converse, yet still does not meet the requirements for an adequate written description of the claimed invention. Applicants propose that the skilled artisan is to modify a known nucleic acid sequence encoding a known protein sequence and that modification would still describe applicants' invention as a PA protein as disclosed. The PA protein of Figure 2 of the specification has specific biological properties dictated by the structure of the protein and the corresponding structure of the structural gene sequence which encodes it. There must be some nexus between the structure of a gene sequence and the structure of the protein encoded, and the function of that encoded protein. However, function cannot be predicted from the modification of the structure of the gene or in this case the gene encoding the protein. Applicants have not shown that, by modifying a reference sequence encoding a reference polypeptide as claimed, will automatically predict the production of a PA protein with the requisite properties. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. Herein, claims directed to the genus of mutants and fragments thereof are unpatentable due to lack of written description for the broad class.

As to claim 50, while the specification supports that "The polynucleotide may be either a DNA or RNA sequence. All forms of DNA whether replicating or non-replicating,

which do not become integrated into the genome, and which are expressible, are within the methods contemplated by the invention." (see page 10, second full paragraph). The teaching does not support the amendment that the first and second isolated polynucleotides become integrated into the genome. Applicants have not provided guidance upon where this new limitation can be found. Assertion of a positive does not provide conception of the opposite or negative. As such, this new limitation is deemed new matter. This issue is best resolved by Applicants pointing to the specification by page and line number where specific written description support can be found.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the

applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 24, 26, 31, 42, 46, 48, 49, 53 and 54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gu et al (Vaccine, 1(4):340-344, Feb 1999; publicly available online January 4, 1999) in view of Brossier et al (Infection and Immunity, 68(4):1781-1786, April 2000), Little et al (Infection and Immunity, 52(2):509-512, 1986), Singh et al (Infection and Immunity 66(7):3447-48, July 1998), Park et al (Protein Expression and Purification, 18:293-302, April 2000) and Donnelly et al (Annu. Rev. Immunol, 15:617-48, 1997).

Gu et al teach protection against anthrax toxin lethality by vaccination with a DNA plasmid encoding anthrax protective antigen (see page 341, column 1, materials and methods). Gu et al teach that DNA vaccination stimulates antibody production and that the anti-PA antibodies were neutralizing for anthrax toxin (see page 343, column 1, Table 1). Gu et al teach that this is the first evidence that a DAN vaccine is able to induce protection against a bacterial toxin and the response was mediated of antigen-specific Th1 and Th2 cytokine secreting cells. Gu et al teach that this facilitates the development of a combination vaccine targeting the LF and EF as well as PA proteins (see page 343, column 2, last paragraph). Gu et al differs by not including with the PA DNA vaccine a combination with a LF DNA vaccine or LF and EF as DNA vaccines where the LF and EF toxins have been detoxified.

Brossier et al teach a vaccine strain of *Bacillus anthrasis* wherein the native pOX1 plasmid of the Sterne strain has native LF substituted with a detoxified LF enzyme where amino acid position 686 is mutated to provide for a mutant totally lacking in metalloproteinase activity and the native EF is substituted with a EF detoxified protein at positions 346 and 353 provided for a protein that totally lacks adenylate cyclase activity. Brossier et al teach that the vaccine strains containing the mutated strains were regulates similarly to the native counterparts. Brossier et al teach that the antibody response to LF

after immunization with mutant *Bacillus anthrasis* is depending upon the production of PA and LF-specific antibody titers are significantly higher if PA is also produced by the bacterium. Brossier et al teach that the involvement of LF-metalloproteinase activity in the immune response could be ruled out because a strong antibody response to LF was also observed with the LF686 producing strain. Brossier et al teach that immunization with the RPACL2 strain PA-EF 346/353-LF686 protected against lethal challenge (page 1785, column 1, first full paragraph). Brossier et al teach that the adjuvant effect of PA on the humoral response requires binding of LF to PA.

Little et al (Infection and Immunity, 52(2):509-512, 1986) teach that the titers against PA, LF, and EF antigens of sera obtained from guinea pigs inoculates with the Sterne spore vaccine suggested that protection of the PA vaccine might be enhanced by the addition of LF or EF toxin components to yield a similar antibody response (page 511, column 1). Little et al teaches that co-immunization of PA and LF provided better protection (6 survivors out of 6 animals) than PA alone (5 survivors out of 6 animals) see page 511, column 2, Table 5 when challenged with the Vollum IB isolate.

Singh et al (Infection and Immunity, 66(7):3447-3448, July 1998) teach that it has been suggested that LF and EF also play an important role in providing immunity (see page 3447, column 3, third paragraph).

Park et al teach the recombinant production of wild type and mutated LF proteins using an expression vector. Park et al teach that the inactive LF mutant (LF687) may provide valuable components of new recombinant vaccines. Park et al teach that "our understanding of the action of the toxin predicts that immunization with inactive LF or EF would augment protection." Singh et al also teach that inclusion of the inactive LF along with PA may provide for a safer vaccine (page 301).

Donnelly et al teach the conventional plasmid components for an effective DNA vector for vaccine use (page 622), including promoters/enhancers for expression of the DNA vaccines in mammalian cells.

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the immunogenic DNA vaccine comprising PA of Gu et al with a DNA vaccine according to Donnelly et al comprising the detoxified LF of Brossier et al and optionally an additional DNA vaccine made according to Donnelly et al comprising the detoxified EF of Brossier et al because Little et al and Singh et al teach that LF and EF may also play an important role in providing immunity, Brossier et al teach that a live vaccine vector strain of *B. anthrasis* comprising PA along with the detoxified LF and EF produced a strong antibody response and Park et al teach that the understanding of action of the toxin predicts that immunization with inactive LF or EF would augment protection and that inclusion of the inactive LF along with PA may provide for a safer vaccine. vaccine production includes a promoter/enhancer for high levels of gene expression in mammalian cells.

PAD Claims 41, 45, 47, 53 and 55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gu et al (Vaccine, 1(4):340-344, Feb 1999; publicly available online January 4, 1999) in view of Brossier et al (Infection and Immunity, 68(4):1781-1786, April 2000), Little et al (Infection and Immunity, 52(2):509-512, 1986), Singh et al (Infection and Immunity 66(7):3447-48, July 1998), Park et al (Protein Expression and Purification, 18:293-302, April 2000) and Donnelly et al (Annu. Rev. Immunol, 15:617-48, 1997) as applied to claims 24, 26, 31, 42, 46, 48, 49, 53 and 54 above, further in view of Glorioso et al (US Patent No 5,998,174, issued December 7, 1999, filed May 12, 1997).

The teachings of Gu et al (Vaccine, 1(4):340-344, Feb 1999; publicly available online January 4, 1999) in view of Brossier et al (Infection and Immunity, 68(4):1781-1786, April 2000), Little et al (Infection and Immunity, 52(2):509-512, 1986), Singh et al (Infection and Immunity 66(7):3447-48, July 1998), Park et al (Protein Expression and Purification, 18:293-302, April 2000) and Donnelly et al (Annu. Rev. Immunol, 15:617-48, 1997) as

combined are set forth supra. The combination differs by not expressing the PA, detoxified LF and optionally detoxified EF using a viral vaccine vector.

Glorioso et al teach multigene HSV viral vaccine vectors capable of expressing a plurality of non-native expression cassettes (see columns 12-13). Glorioso et al teach that the multigene viral vector can comprise any non-native HSV expression cassette and can be applied as a vaccine encoding immunogenic epitopes including those of bacteria. The inoculation can be repeated by booster injections (see column 15, lines 9-37).

It would have been *prima facie* obvious to one of ordinary skill in the art to modify the DNA vaccine as combined supra by cloning the nucleic acid encoding the PA, detoxified LF and optionally the detoxified EF into the multigene HSV viral vector of Glorioso et al because Glorioso et al teach that multiple bacterial immunogens can be produced from a single viral vector and that the multigene HSV vector can also be applied as a vaccine.

Claim 53 is rejected under 35 U.S.C. 103(a) as being unpatentable over Gu et al (Vaccine, 1(4):340-344, Feb 1999; publicly available online January 4, 1999) in view of Brossier et al (Infection and Immunity, 68(4):1781-1786, April 2000), Little et al (Infection and Immunity, 52(2):509-512, 1986), Singh et al (Infection and Immunity 66(7):3447-48, July 1998), Park et al (Protein Expression and Purification, 18:293-302, April 2000) and Donnelly et al (Annu. Rev. Immunol, 15:617-48, 1997) as applied to claims 24, 26, 31, 42, 46, 48, 49, 53 and 54 above, further in view of Felgner et al (US Patent 6,710,035, issued March 23, 2004 with priority to March 21, 1990).

The teachings of Gu et al (Vaccine, 1(4):340-344, Feb 1999; publicly available online January 4, 1999) in view of Brossier et al (Infection and Immunity, 68(4):1781-1786, April 2000), Little et al (Infection and Immunity, 52(2):509-512, 1986), Singh et al (Infection and Immunity 66(7):3447-48, July 1998), Park et al (Protein Expression and Purification, 18:293-302, April 2000) and Donnelly et al (Annu. Rev. Immunol, 15:617-48, 1997) as combined are set forth supra. The combination differs by not expressing the PA,

detoxified LF and optionally detoxified EF using naked mRNA or integration into the host cell genome.

Felgner et al teach methods of delivering an immunogenic polypeptide from a pathogen into the interior of a vertebrate cell *in vivo*. Felgner et al teach the use of naked polynucleotides including DNA and mRNA can be used to express heterologous antigen (see columns 4-6; column 8, lines 30-37; claims 1-26)).

It would have been *prima facie* obvious to one having ordinary skill in the art to substitute mRNA nucleic acids for the DNA plasmids in the composition as combined supra because Felgner et al teach that mRNA can be used to express immunogenic polypeptides in muscle and other non-replicating tissue.

Citation of Relevant Art

The prior art made of record is cumulative to the secondary references above to establish conventional means of delivery of nucleic acid expression vectors to cells for heterologous protein expression:

Powell et al (US Patent 5,877,159, issue March 2, 1999) teach methods for introducing and expressing heterologous genes in animal cells using live invasive bacterial vectors, where the bacteria contain a eukaryotic expression cassette encoding a target gene where the target gene may encode a vaccine antigen.

Ramshaw et al (US Patent 5,866,136, issued Feb, 2, 1999) teaches viral vaccine vectors for expression of heterologous antigens.

Palese et al (US Patent 5,854,037, issued Dec 29, 1998) teach recombinant negative virus RNA templates which may be used to express heterologous gene products in appropriate host cell systems and/or to construct recombinant viruses that express, package and/or present the heterologous gene product. The invention is demonstrated using recombinant influenza virus RNA templates containing a heterologous gene coding sequences in the negative polarity. The recombinant templates with combined with

purified viral RNA-directed RNA polymerase were infectious, replicated and expressed the heterologous gene product. Palese et al teach that the negative strain viruses such as influenzae are attractive candidates for constructing chimeric viruses for use in vaccines because its genetic variability allows for construction of a vast repertoire of vaccine formulations which will stimulate immunity without risk of developing a tolerance.

Status of the Claims

All claims stand rejected.

Conclusion

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy whose telephone number is 571-272-0855. The examiner can normally be reached on M-Th 6:30 am - 6:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on 571-272-0864.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patricia A. Duffy, Ph.D.

Primary Examiner

Art Unit 1645